Medication optimisation in older adults with cancer

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Chapter 4

Severe Fluoropyrimidine Toxicity in Older Adults with Cancer with *DPYD* wild-type

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Abstract

Background

Despite the implementation of *DPYD* genotype-guided dosing, approximately 1 in 3 patients receiving fluoropyrimidine-containing chemotherapy continues to experience severe toxicity. While clinical studies have demonstrated a favorable tolerance among highly selected fit older adults, real-world studies have shown an increased risk of toxicity.

Objective

To identify predictors of severe toxicity or treatment deintensification in older *DPYD* wild-type adults receiving fluoropyrimidine-containing chemotherapy.

Method

Patients wild-type for four tested *DPYD* variants, aged ≥65 years, who participated in a prospective clinical trial investigating genotype-guided individualized fluoropyrimidine dosing, were eligible for the study. The association between tumor-, treatment-, and patient-related characteristics and the occurrence of severe toxicity (grade ≥3, CTCAE v5.0) was analyzed in univariate and multivariate logistic regression analyses. The same analyses were performed for a composite endpoint of severe toxicity or treatment deintensification (including dose reduction, cycle delay or discontinuation).

Results

A total of 311 patients were included. Median age was 71.2 years and 58.8% were male. Grade ≥3 toxicity occurred in 23.2% of patients. In multivariate analysis, none of the characteristics studied were significantly associated with the occurrence of grade ≥3 toxicity. The composite endpoint occurred in 41.2% of patients and was associated with the use of full dose monotherapy in multivariate analysis.

Conclusion

Despite *DPYD* genotype-based dosing, grade ≥3 toxicity and treatment deintensification frequently occur in older patients treated with fluoropyrimidine chemotherapy. No patient-related variables were found to be associated with grade ≥3 toxicity but treatment with dose reduced monotherapy resulted in fewer treatment deintensification or severe toxicity events.

Introduction

For over six decades, fluoropyrimidine-containing chemotherapy has been widely used in various solid tumors, such as breast cancer and gastrointestinal cancers. However, approximately 30% of patients experience severe fluoropyrimidine-associated toxicity, including mucositis, diarrhea, hand-foot syndrome, and bone marrow toxicity [1-3]. Severe fluoropyrimidine-related toxicity may be the result of a deficiency of the main catabolic enzyme dihydropyrimidine dehydrogenase (DPD) which is encoded by the *DPYD* gene and occurs in almost 8% of the general Dutch cancer population [4]. Pre-therapeutic screening of four *DPYD* variant alleles and subsequent dose-individualization reduces the incidence of severe fluoropyrimidine-related toxicity [4,5], yet still 23% of *DPYD* wild-type patients experience severe toxicity and 17% of patients discontinue fluoropyrimidine treatment due to adverse events [4].

In clinical trials, the tolerance of fluoropyrimidine-containing chemotherapy among older patients is comparable to that of younger patients [6-8]. However, it is important to note that elderly patients participating in clinical trials are highly selected and generally in good physical condition, which may not accurately represent for the broader population of older patients in daily clinical practice. In real world settings, older adults often experience more toxicity associated with fluoropyrimidines such as severe diarrhea, stomatitis, and infection [7-9]. Furthermore, van Beek et al. demonstrated that dose reductions were more frequent among patients ≥70 years, compared to younger patients, which could serve as a surrogate marker for lower grade toxicities with a relevant negative impact on the quality of life [7].

Given the increased vulnerability of older adults to severe fluoropyrimidine-related toxicity, the ability to predict the risk of toxicity, in this expanding population becomes increasingly important in clinical practice. Over the past decade, 64% of new cancer diagnoses in the Netherlands were observed in patients ≥65 years [10]. Several studies evaluating various chemotherapy types and regimens have demonstrated that comorbidities and polypharmacy are associated with severe chemotherapy-related toxicity [11-12]. Consequently, the identification of predictors for fluoropyrimidine-associated toxicity would facilitate treatment adaptation and enhance individual treatment outcomes for this frequently utilized group of chemotherapeutic agents.

This study aims to identify patient-, treatment-, and tumor- characteristics associated with severe fluoropyrimidine-associated toxicity or treatment deintensification in *DPYD* wild-type patients aged ≥65 years who participated in a prospective trial.

Method

Study design and setting

This is a retrospective observational cohort study that utilized data derived from a prospective clinical study (NCT02324452) investigating the use of *DPYD*-guided dosing of fluoropyrimidines in cancer patients in 17 hospitals in the Netherlands. A detailed description and primary results of this study have been previously reported [4]. Briefly, cancer patients were prospectively screened for the four most clinically relevant *DPYD* variant alleles. A predefined dose reduction was applied prior to start of fluoropyrimidine treatment in patients identified as *DPYD* variant allele carriers, and the impact of this dose reduction on toxicity was compared to that observed in *DPYD* wild type cancer patients [4].

For the current study, data from six hospitals (three academic and three non-academic) of the original 17 participating study sites was used.

Study population

DPYD wild-type patients aged 65 years and over were included in the present study. All participants had provided written informed consent for the initial study, which included a statement on the use of data for future studies related to the initial one. The Medical Ethical Committee Leiden Den Haag Delft (METC-LDD) has stated that the Medical Research Involving Human Subjects Act (WMO) did not apply and that a separate judgement for ethical approval was not required. Approval for the study, including the extraction of additional information from medical records, was obtained from the respective boards of all six hospitals involved.

Data sources and collection

Data on patient characteristics, tumor characteristics, treatment characteristics, toxicity and treatment deintensification were extracted from the original dataset, where this information was prospectively collected. Patients received capecitabine or fluorouracil, either as monotherapy or in combination with other anticancer agents. Only fluoropyrimidine-associated toxicities were recorded.

Additional patient characteristics obtained from the medical records were collected before start of treatment, with a time frame not exceeding 3 months prior to treatment initiation. These variables included the number of comorbidities, the number of concomitant drugs, serum creatinine (µmol/L), and serum albumin (g/L).

Study outcomes

The primary study outcome was the incidence of grade ≥3 fluoropyrimidine toxicity, assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTC-AE v5.0) [13]. The secondary study outcome was the composite endpoint that included grade ≥3 toxicity and/or treatment deintensification during the first four treatment cycles. Treatment deintensification was a dichotomous outcome defined as the presence or absence of dose reduction, cycle delay, cycle interruption and/or treatment discontinuation after the start of the first cycle. Cycle delay was an increased interval between two treatment cycles and cycle interruption was not completing or interrupting the intended number of days of consecutive chemotherapy treatment in one cycle. Both cycle delay and cycle interruption were registered by the treating oncologist and were extracted from the original dataset.

Statistical analyses

Collected data on patient-, tumor- and treatment-related characteristics were summarized as mean or median for continuous variables and numbers (percentage) for categorical variables. The associations between characteristics and grade ≥3 toxicity or treatment deintensification were examined using univariate logistic regression to calculate the odds ratio (OR) with 95% confidence intervals (95% CI).

Patients were categorized into three groups based on their age at start of the treatment (65-69, 70-74, and ≥75 years). Treatment was categorized as monotherapy or combination chemotherapy. In routine Dutch practice, the initial dose of monotherapy with capecitabine is 2000 - 2500 mg/m^2/ day on days 1-14 within a 21-day cycle. However, when capecitabine is used as a radiosensitizer in combination with radiotherapy, lower doses of 1650 mg/m^2/day are administered specifically on radiotherapy days. For our analysis, we defined the cut-off for normal/high dose range as ≥1800 mg/m^2/day for capecitabine and as ≥2250 mg/m^2/day for 5-fluorouracil, lower doses were considered low dose range. For combination chemotherapy

regimens, a relative dose intensity of ≥80% of the standard chemotherapy regimen was considered a full dose and <80% a reduced dose. Both dose range and dose intensity apply to the dose at the start of the first treatment cycle. BMI was categorized into three groups (<18.5, 18.5- <25, and ≥25 kg/m^2) [14] and the number of comorbidities was grouped into three groups (0-1, 2-3, and ≥4 comorbidities). Polypharmacy was defined as the concurrent use of ≥5 pharmaceutical preparations for systemic use and inhaled drugs that were not related to the cancer treatment. The CKD-EPI-formula was used to calculate an estimation of the glomerular filtration rate (eGFR) to classify renal function (<30 ml/min/1.73 m^2, 30-59 ml/min/1.73 m^2 or ≥60ml/min/1.73 m^2) and serum albumin was used to determine the presence of hypoalbuminemia (serum albumin ≤34 g/L).
Unknown interactions between variables may be present. For example, although not written in the study protocol, oncologists might have started chemotherapy with a lower dose intensity in older, more frail patients, and polypharmacy is likely more present in patients with a high number of comorbidities. To correct for possible unknown interactions between variables, all variables were used in the multivariate logistic regression models for both endpoints as well. A p-value of <0.05 was considered statistically significant. All analyses were performed using IBM SPSS version 28.

Results

In total, 311 *DPYD* wild-type patients aged ≥65 years were included. Median age was 71.0 years (interquartile range (IQR) 67-75) and 58.8% was male. Capecitabine was used in 80.1% of the patients and 43.7% was treated with monotherapy of a fluoropyrimidine agent. The mean BMI was 26.3 kg/m^2 (standard deviation (SD) 4.2), 2.3% of patients were underweight (BMI <18.5 kg/m^2) and 58.2% were overweight (BMI ≥25 kg/m^2). Polypharmacy was present in 37.3% of patients and 24.8% had 4 or more comorbidities. Renal function was moderately reduced (eGFR 30-59 ml/min/1.73 m^2) in 10.9% of patients, and hypoalbuminemia (serum albumin ≤34 g/L) was present in 5.1% of patients. All available patient characteristics are shown in Table 1.
Grade ≥3 toxicity occurred in 23.2% of patients. In Table 2, patient characteristics, and the proportion of patients with grade ≥3 toxicity are presented, as well as the results of the univariate and multivariate analysis. Both the univariate and multivariate analysis showed no significant association with grade ≥3 toxicity for any of the variables, including BMI, number of comorbidities, or polypharmacy.
The composite endpoint of grade ≥3 toxicity and/or treatment deintensification (dose reduction, cycle delay, cycle interruption, discontinuation, or a combination of these) occurred in 41.2%. Cancer stage (p=0.040), chemotherapy regimen (monotherapy or polychemotherapy) (OR 1.73; 95% CI 1.09-2.74; p=0.021), and low dose range (for monotherapy) (OR 0.20; 95% CI 0.09-0.43; p<0.001) were associated with the combined endpoint in the univariate analysis (Table 3). For cancer stage, this was mainly driven by the metastasized stage which exhibited a two times higher odd ratio compared to the local and locally advanced stages. In the multivariate analysis, only the association with dose range remained significant (OR 0.28; 95% CI 0.16-0.49; p<0.001 for low dose). The results of the univariate and multivariate analyses are shown in Table 3.
We also performed subgroup analyses for patients without concurrent radiotherapy - as these patients received low dose fluoropyrimidines – and for patients receiving monotherapy – as toxicity could be caused by concurrent chemotherapeuticals. We found significant associations in patients receiving monotherapy for treatment deintensification for

metastasized stage (univariate analysis), locally advanced stage (multivariate analysis) and low dose range (univariate and multivariate analyses). The results are described in Supplementary tables S1, S2, S3, and S4.

Table 1. Patient characteristics

	ALL (N=311)
Age, years (median (IQR))	71.0 (8)
65-69 years	132 (42.4%)
70-74 years	92 (29.6%)
75+ years	87 (28.0%)
Sex	
Male	183 (58.8%)
Female	128 (41.2%)
Primary tumour	
Colorectal	202 (65.0%)
Breast	29 (9.3%)
Gastric	24 (7.7%)
Genitourinary	21 (6.8%)
Oesophageal	9 (2.9%)
Pancreas	8 (2.6%)
Other‡	13 (4.2%)
Missing	5 (1.6%)
Cancer stage	
Local	55 (17.7%)
Locally advanced	156 (50.2%)
Metastasized	96 (30.9%)
Missing	4 (1.3%)
Drug	
Capecitabine	249 (80.1%)
5-fluorouracil	62 (19.9%)
Chemotherapy regimen	
Monotherapy	136 (43.7%)
Dose range normal/ high	*47 (15.1%)*
Dose range low	*89 (28.6%)*
Polychemotherapy†	175 (56.3%)
Full dose	*163 (52.4%)*
Reduced dose	*12 (3.9%)*
Concurrent radiotherapy	
No	185 (59.5%)
Yes	126 (40.5%)
BMI (mean (95% CI))	26.3 (25.8-26.8)
Underweight (<18.5 kg/m^2)	7 (2.3%)
Normal (18.5 – <25 kg/m^2)	119 (38.3%)
Overweight (≥25.0 kg/m^2)	181 (58.2%)
Missing	4 (1.3%)

Table 1 continued

	ALL (N=311)
Number of comorbidities (mean (95% CI))	2.3 (2.1-2.5)
0-1	125 (40.2%)
2-3	108 (34.7%)
≥4	77 (24.8%)
Missing	1 (0.3%)
Polypharmacy	
Yes (≥5 concomitant drugs)	112 (36.0%)
No	189 (60.8%)
Missing	10 (3.2%)
eGFR	
30-59 ml/min/1.73m2	34 (10.9%)
≥60 ml/min/1.73m2	276 (88.7%)
Missing	1 (0.3%)
Albumine	
Hypoalbuminemia (≤34 g/l)	16 (5.1%)
Normal (35-53 g/l)	264 (84.9%)
Missing	31 (10.0%)

Abbreviations: IQR – interquartile range; BMI – body mass index; 95% CI – 95% confidence interval; eGFR – estimated glomerular filtration rate

‡head and neck, skin, lung, vulvar, galbladder; †regimen of a fluoropyrimidine in combination with one or more other chemotherapeutical agents First course dose range low = capecitabine: 2dd <900mg/m^2. First course monotherapy with fluorouracil was never reduced. Dose intensity of first course polychemotherapy was considered reduced when <80% of the usual schedule was administered.

Table 2. Analysis of associations between patient characteristics and occurrence of grade ≥3 toxicity

		Univariate analysis		Multivariate anaysis	
	Toxicity (%)	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
All	23.2				
Age			0.795		0.758
65-69 years	24.2	1.00 (ref)			
70-74 years	20.7	0.81 (0.43 – 1.55)		0.79 (0.40 – 1.59)	
75+ years	24.1	0.99 (0.53 – 1.87)		1.02 (0.51 – 2.04)	
Sex			0.518		0.504
Female	25.0	1.00 (ref)			
Male	21.9	0.84 (0.49 – 1.43)		0.82 (0.46 – 1.46)	
Cancer stage			0.962		0.972
Local	21.8	1.00 (ref)			
Locally advanced	22.4	1.04 (0.49 – 2.18)		0.87 (0.39 – 1.94)	
Metastasized	25.1	1.19 (0.54 – 2.63)		0.81 (0.33 – 1.98)	
Missing	25.0	1.19 (0.11 – 12.55)		0.74 (0.06 – 8.94)	
Drug			0.905		0.470
Capecitabine	23.3	1.00 (ref)			
5-fluorouracil	22.6	0.96 (0.49 – 1.87)		0.74 (0.32 – 1.68)	
Chemotherapy regimen			0.080		0.098
Monotherapy	18.4	1.00 (ref)			
Polychemotherapy	26.9	1.63 (0.94– 2.82)		1.78 (0.90 – 3.501)	
Dose range capecitabine/5-FU (monotherapy)			0.867		0.424
Normal/high dose	19.1	1.00 (ref)			
Low dose	18.0	0.925 (0.37 – 2.29)		0.77 (0.41 – 1.46)	
Dose intensity polychemotherapy			0.601		0.318
Full dose	26.4	1.00 (ref)			
Reduced dose	33.3	1.40 (0.40 – 4.87)		1.58 (0.64 – 3.89)	

Table 2 continued

	Toxicity (%)	Univariate analysis Odds ratio (95% CI)	p-value	Multivariate anaysis Odds ratio (95% CI)	p-value
BMI			0.434		0.334
Underweight (<18.5 kg/m^2)	42.9	2.13 (0.45– 10.05)		2.39 (0.45 – 12.70)	
Normal (18.5 – <25 kg/m^2)	26.1	1.00 (ref)			
Overweight (≥25.0 kg/m^2)	20.4	0.73 (0.42 – 1.26)		0.69 (0.38 – 1.25)	
Missing	25.0	0.95 (0.10 – 9.44)		1.79 (0.13 – 23.78)	
Number of comorbidities			0.472		0.919
0-1	20.8	1.00 (ref)			
2-3	21.3	1.03 (0.55 – 1.94)		0.97 (0.48 – 1.93)	
≥4	29.9	1.62 (0.85– 3.11)		1.25 (0.56 – 2.82)	
Missing	0.0	n/a		n/a	
Polypharmacy (≥5 drugs)			0.522		0.740
No	21.2	1.00 (ref)			
Yes	26.8	1.36 (0.79– 2.35)		1.27 (0.66 – 2.42)	
Missing	20.0	0.93 (0.19 – 4.56)		0.85 (0.15 – 4.75)	
Renal function			0.666		0.600
eGFR 30-59 ml/min/1.73 m^2	33.3	1.44 (0.65 – 3.17)		1.57 (0.66 – 3.76)	
eGFR ≥60 ml/min/1.73 m^2	23.6	1.00 (ref)			
Missing	0.0	n/a		n/a	
Serum albumine			0.7437		0.420
Normal (35-53 g/l)	22.0	1.00 (ref)			
Hypoalbuminemia (≤34 g/l)	25.0	1.18 (0.37 – 3.81)		1.12 (0.33 – 3.82)	
Missing	32.3	1.69 (0.75 – 3.79)		1.79 (0.75 – 4.25)	

Abbreviations: 5-FU – fluorouracil; BMI – body mass index; eGFR – estimated glomerular filtration rate; n/a – not applicable

Table 3. Analysis of association between patient characteristics and occurrence of grade ≥3 toxicity and/or treatment deintensification (≤4 cycles)

	Outcome (%)	Univariate analysis Odds ratio (95% CI)	p-value	Multivariate anaysis Odds ratio (95% CI)	p-value
All	41.2				
Age			0.888		0.876
65-69 years	41.7	1.00 (ref)			
70-74 years	39.1	0.90 (0.52 – 1.55)		1.02 (0.55 – 1.89)	
75+ years	42.5	1.04 (0.60 – 1.79)		1.17 (0.62 – 2.20)	
Sex			0.087		0.149
Female	46.9	1.00 (ref)			
Male	37.2	0.67 (0.42 – 1.06)		0.68 (0.41 – 1.15)	
Cancer stage			**0.040**		0.818
Local	34.5	1.00 (ref)			
Locally advanced	36.5	1.09 (0.57 – 2.08)		0.85 (0.41 – 1.76)	
Metastasized	53.1	2.15 (1.08 – 4.26)		1.03 (0.47 – 2.30)	
Missing	25.0	0.63 (0.06 – 6.49)		0.41 (0.03 – 5.21)	
Drug			0.311		0.778
Capecitabine	42.6	1.00 (ref)			
5-fluorouracil	35.5	0.74 (0.42 – 1.32)		0.90 (0.43 – 1.90)	
Chemotherapy regimen			**0.021**		0.092
Monotherapy	33.8	1.00 (ref)			
Polychemotherapy	46.9	1.73 (1.09 – 2.74)		1.68 (0.92 – 3.06)	
Dose range capecitabine/5-FU (monotherapy)			**<0.001**		**<0.001**
Normal/high dose	57.4	1.00 (ref)			
Low dose	21.3	0.20 (0.09 – 0.43)		0.28 (0.16 – 0.49)	
Dose intensity polychemotherapy			0.413		0.113
Full dose	46.0	1.00 (ref)			
Reduced dose	58.3	1.64 (0.50 – 5.39)		1.95 (0.85 – 4.44)	

Table 3 continued

	Outcome (%)	Univariate analysis Odds ratio (95% CI)	p-value	Multivariate anaysis Odds ratio (95% CI)	p-value
BMI			0.738		0.920
Underweight (<18.5 kg/m^2)	57.1	1.78 (0.38 – 8.30)		1.75 (0.33 – 9.35)	
Normal (18.5 – <25 kg/m^2)	42.9	1.00 (ref)			
Overweight (≥25.0 kg/m^2)	39.2	0.86 (0.54 – 1.38)		1.07 (0.62 – 1.83)	
Missing	50.0	1.33 (0.18 – 9.79)		1.46 (0.12 – 18.46)	
Number of comorbidities			0.568		0.889
0-1	40.0	1.00 (ref)			
2-3	38.0	0.92 (0.54 – 1.56)		0.96 (0.52 – 1.77)	
≥4	48.1	1.39 (0.78 – 2.46)		1.26 (0.60 – 2.64)	
Missing	0.0	n/a		n/a	
Polypharmacy (≥5 drugs)			0.732		0.702
No	39.7	1.00 (ref)			
Yes	42.9	1.14 (0.71 – 1.83)		1.01 (0.56 – 1.82)	
Missing	50.0	1.52 (0.43 – 5.43)		1.88 (0.43 – 8.24)	
Renal function					0.915
eGFR 30-59 ml/min/1.73 m^2	38.2	0.88 (0.42 – 1.83)		0.83 (0.36 – 1.94)	
eGFR ≥60 ml/min/1.73 m^2	41.3	1.00 (ref)			
Missing	100.0	n/a		n/a	
Serum albumine			0.755		0.759
Normal (35-53 g/l)	40.5	1.00 (ref)			
Hypoalbuminemia (≤34 g/l)	50.0	1.47 (0.53 – 4.03)		1.47 (0.48 – 4.51)	
Missing	41.9	1.06 (0.50 – 2.25)		0.88 (0.37 – 2.10)	

Abbreviations: 5-FU – fluorouracil; BMI – body mass index; eGFR – estimated glomerular filtration rate

Discussion

This study is one of the first studies focusing on identifying predictors for severe toxicity in older patients receiving fluoropyrimidine therapy. We demonstrated that 23.2% of *DPYD* wild type patients older than 65 years experienced severe fluoropyrimidine-related toxicity and an additional 18% of patients that did not experience severe (grade ≥3) toxicity still required treatment deintensification. Our analysis for predictors of severe fluoropyrimidine-related toxicity revealed no significant associations with any of the variables investigated.

Several previous studies have investigated the incidence of severe fluoropyrimidine-related toxicity in different patient populations, with reported rates ranging from 12-53% [4,6,9]. Studies specifically focusing on older patients found similar ranges from 22-62% of severe toxicity, and rates of treatment deintensification ranging from 26-57% [15-19]. In our study, incidence of severe toxicity was relatively low, as we included only *DPYD* wild-type patients, who are at lower risk of toxicity [20-23]. Also, monotherapy was relatively frequently prescribed compared to previous studies [7], which could explain the lower toxicity rate. Monotherapy is generally associated with lower toxicity than polychemotherapy [20,21,23]. For example, a previous study showed that severe fluoropyrimidine-related toxicity occurred only in 12% of older patients treated with capecitabine monotherapy [24].

In the original study [4], only fluoropyrimidine-associated toxicities were registered. However, for polychemotherapy an overlap may occur for some types of toxicity between the fluoropyrimidine and concurrently administered chemotherapeutical agent. As a result, fluoropyrimidine toxicity may be overestimated in patients receiving polychemotherapy. Additional analyses showed that overall 23% of patients experienced grade ≥3 toxicity and 18% for patients receiving fluoropyrimidine monotherapy. For treatment deintensification, the results were 41% resp. 34%.

We observed no significant difference in the incidence of severe toxicity across older age subgroups. This is in line with the results of a study by Feliú et al., in which no significant difference in the incidence of severe capecitabine toxicity was observed between patients over 65 years of age and those aged 70 or 80 years and over [24]. Similarly, D'Andre et al. also reported no significant difference in severe toxicity between different age groups in four randomized clinical trials with more fit patients than a real-world population [9].

The composite endpoint of grade ≥3 toxicity and/or treatment deintensification was observed in 41% of patients in our study, considering the impact of lower grade toxicity as well. We hypothesized that the presence of grade 2 toxicity, such as hand-foot syndrome or mucositis, in older patients undergoing fluoropyrimidine-based chemotherapy may significantly impact their independence and quality of life to the extent that they may opt to discontinue treatment at full dosage. This decision may be confounded by the presence of comorbidities and concomitant use of multiple medications, resulting in treatment mitigation even in cases of low-grade toxicity. Our findings suggest that low-grade toxicity should not be overlooked in older adults receiving chemotherapy, as it may have significant clinical relevance in addition to severe toxicity. In a previous real-world study conducted in the Netherlands, dose adjustments due to capecitabine-induced toxicity were reported in 83% of patients over 70 years of age [7]. Of note, *DPYD*-guided dosing was not yet in clinical practice during that study, and patients with upfront dose reductions were excluded from the analysis. Additionally, a higher proportion of patients received polychemotherapy (68%) compared to our study (56%). These differences may have contributed to a higher incidence of toxicity in the study described by van Beek *et al.*, resulting in more frequent dose reductions compared to our study. In the X-ACT trial, dose modifications (dose reduction, delay, or interruption) were required in 61%

and 65% of patients ages ≥70 years for fluorouracil and capecitabine respectively [25]. Patients in the X-ACT trial received monotherapy with a fluoropyrimidine agent and the high dose of capecitabine 2500 mg/m^2 daily was used, whereas in our study, 44% of patients received monotherapy and the average dose was lower. In our study, a relatively large proportion of patients received concurrent radiotherapy, in which capecitabine is given in a low dose as a radiosensitizer. As such, capecitabine causes severe toxicity only in 14% of patients and leads to some form of treatment deintensification in up to 10% of *DPYD* wild type carriers (dose reductions 4%; interruptions 5%; prematurely stopped 10%) [26]. Also, a possibly age-related decrease in treatment tolerance may have become obvious when comparing older adults with younger patients instead of the comparison of patients aged 65-74 years with those aged ≥75 years in this study.

Patients who started with a reduced dose in a polychemotherapy schedule, did not experience more severe toxicity, but they did experience more often de-intensification of treatment, possibly because of initial frailty. In our study, 4% of patients started treatment with a reduced dose, presumably as precautionary measure from the oncologist in more frail patients. In a real-world study, other investigators found that 15% of fit patients received chemotherapy undertreatment and 33% of frail patients were overtreated. Grade 3-5 toxicity occurred significantly less in undertreated patients (24%) compared to appropriately treated patients (31%) or overtreated patients (40%), but treatment de-intensification was not assessed [11]. In an additional analysis, we tested whether certain subgroups of patients – e.g. those with lower BMI or higher age – were more likely to receive a reduced starting dose but we did not find any associations (data not shown). Patients with a BMI <18.5 kg/m^2 seemed to experience twice as much toxicity as patients with normal BMI and nearly three times more than those with a BMI ≥25 kg/m^2, but this was not significant. Underweight patients may have less functional reserve in that they may suffer more severe consequences of vomiting, diarrhea, and decreased food intake that are caused by chemotherapy. Hurria *et al.* also found a lower BMI to be associated with increased toxicity, although that was only shown for a BMI ≤26.5 kg/m^2 compared to BMI >26.5 kg/m^2 [27]. Exposing underweight patients to chemotherapy appears to put them in a high risk of severe toxicity [28,29]. Of note, it was recently demonstrated that decreased BMI was associated with increased risk of developing fluoropyrimidine-induced cardiotoxicity [30]. The observation of a higher incidence of severe toxicity in patients undergoing polychemotherapy is consistent with our expectations, as the use of polychemotherapy is known to be associated with increased risk of adverse events [20-23].

The finding that none of the investigated factors were associated with severe toxicity implies that a major driver of fluoropyrimidin-associated toxicity has been dealt with by using *DPYD*-guided dosing and is also effective in older adults.

The retrospective nature of this study presents a significant limitation, as it restricted the variables for analysis. Furthermore, no geriatric assessment data were available to assess frailty of patients. Frailty is a commonly recognized age-related condition that stems from the progressive deterioration of multiple organ systems, leading to a reduced ability to withstand stressors such as chemotherapy. This is thought to be caused by the complex interplay between biological, psychological, and social factors and has been associated with adverse health outcomes [27,31,32]. The incorporation of geriatric assessments would have provided valuable information tailored to the needs of older patients. This has previously been confirmed by two randomized clinical trials in which it was studied whether toxicity could be reduced by geriatric assessment-guided treatment decisions in patients ≥70 years treated

with chemotherapy [33,34]. Both studies showed that grade ≥3 toxicity could significantly be reduced by using personalized treatment in older patients treated with chemotherapy based on the outcome of geriatric assessments without affecting the one-year survival [33,34]. Unfortunately, the availability of such data was limited. Future research should prioritize the inclusion of geriatric assessments, preferably in a prospective study, to obtain a comprehensive understanding of potential predictive factors for severe toxicity in older patients treated with fluoropyrimidines. Furthermore, previous studies have shown that tolerance of fluoropyrimidines among elderly is comparable to that of younger patients, possibly due to the inclusion of relatively fit elderly in clinical trials [6-8]. The prevalence of severe fluoropyrimidine toxicity within elderly patients our study (23.2%) implies a potential parallel with the complete cohort of the Alpe-DPD study in which the prevalence of severe toxicity was 23%. Therefore, inclusion of real-world data without selection of elderly patients based on WHO status or physical condition could provide valuable information in future studies. Another limitation of this study is the inclusion of patients with chemoradiaton, as these patients receive a lower dose of fluoropyrimidines. Although we corrected for low dose versus normal/high dose in patients receiving monotherapy, the results may be confounded by retaining these patients in the analysis. In addition, the relatively small sample size may have affected the power to detect significant associations between potential predictive factors and severe fluoropyrimidine-related toxicity in older patients. Hence, the findings of this study should be interpreted with caution and future prospective studies with larger samples sizes are needed to confirm the demonstrated trends towards a higher occurrence of severe toxicity and establish more robust evidence. Ideally, such studies should also include *DPYD*-variant allele carriers who receive adjusted doses of fluoropyrimidines. However, a study to investigate frailty or geriatric conditions as possible predictors for severe toxicity or treatment tolerance and which also includes *DPYD*-variant allele carriers would encounter the challenge of including a large number of participants to be able to draw reliable conclusions.

Conclusion

Despite *DPYD* genotype-guided dosing, which has been shown to reduce fluoropyrimidine-associated toxicity, a substantial proportion of older adults treated with fluoropyrimidines still experience severe toxicity and treatment deintensification. Our study most likely did not have sufficient power to identify significant associations between patient-related predictors and toxicity. Future real-world studies, preferably prospective, are needed to investigate these predictive factors. Additionally, these studies should include specific geriatric parameters and the tolerability of low-grade toxicity to gain a better understanding of the complex interaction between aging, cancer, and fluoropyrimidine-related toxicity and ultimately improve the efficacy and safety of fluoropyrimidine treatment in older adults.

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Supplementary tables

Table S1. Subgroup analysis of associations between patient characteristics and occurrence of grade ≥3 toxicity in patients without concurrent radiotherapy (n=185)

		Univariate analysis		Multivariate anaysis	
	Toxicity (%)	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
All	25.9				
Age			0.966		0.747
65-69 years	25.0	1.00 (ref)			
70-74 years	26.9	1.11 (0.50 – 2.45)		1.07 (0.43 – 2.66)	
75+ years	26.4	1.08 (0.49 – 2.38)		1.42 (0.56 – 3.57)	
Sex			0.739		0.496
Female	27.2	1.00 (ref)			
Male	25.0	0.89 (0.46 – 1.73)		0.77 (0.36 – 1.65)	
Cancer stage			0.842		0.975
Local	25.0	1.00 (ref)			
Locally advanced	27.8	1.15 (0.37 – 3.59)		0.83 (0.24 – 2.83)	
Metastasized	24.2	0.96 (0.31 – 2.93)		0.79 (0.23 – 2.76)	
Missing	50.0	3.00 (0.16 – 57.37)		1.24 (0.05 – 31.68)	
Drug			0.136		0.085
Capecitabine	28.0	1.00 (ref)			
5-fluorouracil	14.3	0.43 (0.14 – 1.30)		0.33 (0.10 – 1.16)	
Chemotherapy regimen			0.354		0.090
Monotherapy	21.2	1.00 (ref)			
Polychemotherapy	27.8	1.44 (0.67 – 3.09)		2.47 (0.87 – 7.04)	
Dose range capecitabine/5-FU (monotherapy)			0.931		0.239
Normal/high dose	20.9	1.00 (ref)			
Low dose	22.2	1.08 (0.19 – 6.12)		0.53 (0.19 – 1.52)	
Dose intensity polychemotherapy			0.512		0.479
Full dose	21.6	1.00 (ref)			
Reduced dose	20.0	1.54 (0.42 – 5.61)		1.57 (0.45 – 5.53)	

Table S1 continued

		Univariate analysis		Multivariate anaysis	
	Toxicity (%)	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
BMI			0.439		0.162
Underweight (<18.5 kg/m^2)	28.4	2.52 (0.47 – 13.42)		3.46 (0.50 – 23.72)	
Normal (18.5 – <25 kg/m^2)	50.0	1.00 (ref)			
Overweight (≥25.0 kg/m^2)	22.1	0.72 (0.36 – 1.42)		0.55 (0.25 – 1.21)	
Missing	33.3	1.26 (0.11 – 14.59)		1.79 (0.11 – 28.32)	
Number of comorbidities			0.258		0.611
0-1	22.2	1.00 (ref)			
2-3	21.7	0.97 (0.42 – 2.22)		0.93 (0.36 – 2.39)	
≥4	36.5	2.02 (0.92 – 4.45)		1.74 (0.61 – 4.94)	
Missing	0	n/a		n/a	
Polypharmacy (≥5 drugs)			0.576		0.627
No	23.3	1.00 (ref)			
Yes	30.1	1.42 (0.72 – 2.80)		1.51 (0.66 – 3.45)	
Missing	22.2	0.94 (0.18 – 4.83)		1.28 (0.20 – 8.12)	
Renal function			0.764		0.889
eGFR 30-59 ml/min/1.73 m^2	33.3	1.48 (0.52 – 4.18)		1.37 (0.38 – 4.91)	
eGFR ≥60 ml/min/1.73 m^2	25.3	1.00 (ref)			
Missing	0	n/a		n/a	
Serum albumine			0.327		0.339
Normal (35-53 g/l)	24.2	1.00 (ref)			
Hypoalbuminemia (≤34 g/l)	25.0	1.05 (0.27 – 4.06)		1.14 (0.26 – 4.94)	
Missing	40.0	2.09 (0.79 – 5.50)		2.28 (0.76 – 6.81)	

Abbreviations: 5-FU – fluorouracil; BMI – body mass index; eGFR – estimated glomerular filtration rate; n/a – not applicable

Table S2. Subgroup analysis of association between patient characteristics and occurrence of grade ≥3 toxicity and/or treatment deintensification (≤4 cycles) in patients without concurrent radiotherapy (n=185)

		Univariate analysis		Multivariate anaysis	
	Outcome (%)	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
All	53.0				
Age			0.724		0.723
65-69 years	51.2	1.00 (ref)			
70-74 years	57.7	1.30 (0.64 – 2.62)		1.39 (0.61 – 3.14)	
75+ years	50.9	0.99 (.49 – 1.98)		1.10 (0.50 – 2.42)	
Sex			0.225		0.231
Female	58.0	1.00 (ref)			
Male	49.0	0.70 (0.39 – 1.25)		0.66 (0.34 – 1.30)	
Cancer stage			0.989		0.945
Local	50.0	1.00 (ref)			
Locally advanced	54.2	1.18 (0.44 – 3.19)		0.80 (0.26 – 2.48)	
Metastasized	52.7	1.12 (0.42 – 2.94)		0.82 (0.27 – 2.56)	
Missing	50.0	1.00 (0.06 – 18.30)		0.40 (0.02 – 9.73)	
Drug			**0.020**		0.090
Capecitabine	56.7	1.00 (ref)			
5-fluorouracil	32.1	0.36 (0.15 – 0.85)		0.42 (0.15 – 1.15)	
Chemotherapy regimen			0.422		0.572
Monotherapy	57.7	1.00 (ref)			
Polychemotherapy	51.1	0.77 (0.40 – 1.47)		1.28 (0.54 – 3.01)	
Dose range capecitabine/5-FU (monotherapy)			0.381		**0.006**
Normal/high dose	60.5	1.00 (ref)			
Low dose	44.4	0.52 (0.12 – 2.23)		0.29 (0.12 – 0.69)	
Dose intensity polychemotherapy			0.391		0.392
Full dose	50.0	1.00 (ref)			
Reduced dose	63.6	1.75 (0.49 – 6.29)		1.60 (0.55 – 4.69)	

Table S2 continued

		Univariate analysis		Multivariate anaysis	
	Outcome (%)	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
BMI			0.865		0.926
Underweight (<18.5 kg/m^2)	66.7	1.77 (0.31 – 10.20)		1.53 (0.22 – 10.88)	
Normal (18.5 – <25 kg/m^2)	53.1	1.00 (ref)			
Overweight (≥25.0 kg/m^2)	51.6	0.94 (0.52 – 1.70)		0.86 (0.44 – 1.70)	
Missing	66.7	1.77 (0.15 – 20.27)		0.96 (0.07 – 13.64)	
Number of comorbidities			0.552		0.368
0-1	51.4	1.00 (ref)			
2-3	48.3	0.89 (0.45 – 1.76)		0.87 (0.39 – 1.96)	
≥4	61.5	1.51 (0.73 – 3.13)		1.91 (0.74 – 4.94)	
Missing	0	n/a		n/a	
Polypharmacy (≥5 drugs)			0.979		0.628
No	52.4	1.00 (ref)			
Yes	53.4	1.04 (0.57 – 1.90)		1.11 (0.53 – 2.30)	
Missing	55.6	1.13 (0.29 – 4.47)		2.25 (0.43 – 11.71)	
Renal function			0.971		0.817
eGFR 30-59 ml/min/1.73 m^2	50.0	0.89 (0.34 – 2.35)		0.69 (0.22 – 2.18)	
eGFR ≥60 ml/min/1.73 m^2	53.0	1.00 (ref)			
Missing	100.0	n/a		n/a	
Serum albumine			0.905		0.704
Normal (35-53 g/l)	52.3	1.00 (ref)			
Hypoalbuminemia (≤34 g/l)	58.3	1.28 (0.39 – 4.20)		1.71 (0.44 – 6.68)	
Missing	55.0	1.12 (0.44 – 2.85)		0.86 (0.29 – 2.50)	

Abbreviations: 5-FU – fluorouracil; BMI – body mass index; eGFR – estimated glomerular filtration rate

Table S3. Analysis of associations between patient characteristics and occurrence of grade ≥3 toxicity in patients receiving fluoropyrimidine monotherapy (N=136)

		Univariate analysis		Multivariate anaysis	
	Toxicity (%)	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
All	18.4				
Age			0.647		0.602
65-69 years	21.3	1.00 (ref)			
70-74 years	14.3	0.62 (0.21 – 1.78)		0.56 (0.18 – 1.75)	
75+ years	20.0	0.93 (0.33 – 2.63)		0.82 (0.25 – 2.68)	
Sex			0.917		0.645
Female	18.8	1.00 (ref)			
Male	18.1	0.96 (0.40 – 2.28)		1.27 (0.46 – 3.55)	
Cancer stage			0.776		0.958
Local	13.6	1.00 (ref)			
Locally advanced	17.5	1.34 (0.35 – 5.17)		1.52 (0.35 – 6.72)	
Metastasized	24.2	2.03 (0.47 – 8.68)		1.47 (0.24 – 9.08)	
Missing	0.0	n/a		n/a	
Drug			0.288		0.125
Capecitabine	17.9	1.00 (ref)			
5-fluorouracil	50.0	4.58 (0.28 – 75.89)		14.64 (0.48 – 451.15)	
Dose range capecitabine/5-FU			0.925		0.679
Normal/high dose	19.1	1.00 (ref)			
Low dose	18.0	0.93 (0.37 – 2.29)		0.79 (0.26 – 2.40)	
BMI			0.429		0.327
Underweight (<18.5 kg/m^2)	40.0	4.67 (0.64 – 33.91)		7.15 (0.73 – 70.49)	
Normal (18.5 – <25 kg/m^2)	12.5	1.00 (ref)			
Overweight (≥25.0 kg/m^2)	20.3	1.78 (0.64 – 4.91)		1.93 (0.65 – 5.79)	
Missing	25.0	2.33 (0.21 – 26.23)		3.11 (0.23 – 41.61)	

Table S3 continued

		Univariate analysis		Multivariate anaysis	
	Toxicity (%)	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Number of comorbidities			0.979		0.580
0-1	17.7	1.00 (ref)			
2-3	19.2	1.10 (0.43 – 2.85)		0.96 (0.30 – 3.00)	
≥4	18.2	1.03 (0.29 – 3.65)		0.43 (0.07 – 2.48)	
Missing	n/a	n/a		n/a	
Polypharmacy (≥5 drugs)			0.586		0.612
No	16.1	1.00 (ref)			
Yes	21.7	1.45 (0.59 – 3.58)		1.65 (0.48 – 5.68)	
Missing	33.3	2.61 (0.22 – 30.75)		3.07 (0.18 – 52.37)	
Renal function			0.779		0.650
eGFR 30-59 ml/min/1.73 m^2	25.0	1.56 (0.46 – 5.30)		1.96 (0.48 – 8.05)	
eGFR ≥60 ml/min/1.73 m^2	17.6	1.00 (ref)			
Missing	0.0	n/a		n/a	
Serum albumine			0.641		0.872
Normal (35-53 g/l)	17.6	1.00 (ref)			
Hypoalbuminemia (≤34 g/l)	33.3	2.33 (0.40 – 13.58)		1.77 (0.21 – 15.03)	
Missing	18.2	1.04 (0.21 – 5.15)		1.01 (0.17 – 5.96)	

Abbreviations: 5-FU – fluorouracil; BMI – body mass index; eGFR – estimated glomerular filtration rate; n/a – not applicable

Table S4. Analysis of association between patient characteristics and occurrence of grade ≥3 toxicity and/or treatment deintensification (≤4 cycles) in patients receiving fluoropyrimidine monotherapy (N=136)

		Univariate analysis		Multivariate anaysis	
	Outcome (%)	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
All	33.8				
Age			0.620		0.743
65-69 years	36.2	1.00 (ref)			
70-74 years	28.6	0.71 (0.30 – 1.67)		0.69 (0.25 – 1.94)	
75+ years	37.5	1.06 (0.44 – 2.54)		0.98 (0.33 – 2.98)	
Sex			0.116		0.958
Female	40.6	1.00 (ref)			
Male	27.8	0.56 (0.27 – 1.15)		0.98 (0.39 – 2.45)	
Cancer stage			**0.017**		0.940
Local	22.7	1.00 (ref)			
Locally advanced	27.5	1.29 (0.42 – 3.92)		1.46 (0.39 – 5.49)	
Metastasized	57.6	4.61 (1.37 – 15.52)		1.14 (0.22 – 6.01)	
Missing	0.0	n/a		n/a	
Drug			0.632		0.065
Capecitabine	33.6	1.00 (ref)			
5-fluorouracil	50.0	1.98 (0.12 – 32.36)		24.73 (0.82 – 750.37)	
Dose range capecitabine/5-FU (monotherapy)			**<0.001**		**<0.001**
Normal/high dose	57.4	1.00 (ref)			
Low dose	21.3	0.20 (0.09 – 0.43)		0.10 (0.03 – 0.30)	
BMI			0.287		0.065
Underweight (<18.5 kg/m^2)	60.0	4.50 (0.67 – 30.23)		8.56 (0.86 – 85.15)	
Normal (18.5 – <25 kg/m^2)	25.0	1.00 (ref)			
Overweight (≥25.0 kg/m^2)	36.7	1.74 (0.78 – 3.86)		3.63 (1.27 – 10.40)	
Missing	50.0	3.00 (0.38 – 23.68)		3.19 (0.28 – 35.77)	

Table S4 continued

		Univariate analysis		Multivariate anaysis	
	Outcome (%)	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Number of comorbidities			0.745		0.140
0-1	33.9	1.00 (ref)			
2-3	36.5	1.12 (0.52 – 2.43)		1.02 (0.36 – 2.87)	
≥4	27.3	0.73 (0.25 – 2.15)		0.22 (0.04 – 1.22)	
Missing	n/a	n/a		n/a	
Polypharmacy (≥5 drugs)			0.418		0.325
No	31.0	1.00 (ref)			
Yes	37.0	1.30 (0.61 – 2.76)		1.49 (0.47 – 4.77)	
Missing	66.7	4.44 (0.39 – 51.15)		14.87 (0.38 – 584.47)	
Renal function			0.982		0.973
eGFR 30-59 ml/min/1.73 m^2	31.3	0.90 (0.29 – 2.76)		0.84 (0.20 – 3.51)	
eGFR ≥60 ml/min/1.73 m^2	33.6	1.00 (ref)			
Missing	100.0	n/a		n/a	
Serum albumine			0.642		0.339
Normal (35-53 g/l)	33.6	1.00 (ref)			
Hypoalbuminemia (≤34 g/l)	50.0	1.98 (0.38 – 10.23)		3.51 (0.35 – 35.50)	
Missing	27.3	0.74 (0.19 – 2.95)		0.38 (0.06 – 2.63)	

Abbreviations: 5-FU – fluorouracil; BMI – body mass index; eGFR – estimated glomerular filtration rate